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## **Racial variation in umbilical cord blood leptin concentration in male babies**

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**Abstract:** Background: We hypothesize that racial differences in utero contribute to the racial disparity in prostate cancer risk. Leptin is a candidate for evaluating this hypothesis because it influences fetal development and newborn growth. Methods: We measured leptin concentration by ELISA in venous cord blood collected from 70 African-American and 37 white male full-term babies. We measured sex steroid hormones and insulin-like growth factor (IGF) axis concentrations previously. Separately by race, we calculated the geometric mean leptin concentration and estimated the geometric mean adjusted for birth and placental weights, mother's age and parity, time of day and season of birth, and sex steroid hormone and IGF axis concentrations by linear regression. Results: Leptin was positively correlated with birth ( $r = 0.34$ ) and placental ( $r = 0.25$ ) weights, IGF-1 ( $r = 0.21$ ), and IGF binding protein-3 ( $r = 0.29$ ) adjusting for race. Unadjusted geometric mean leptin did not differ ( $P = 0.92$ ) between African Americans (5,280 pg/mL; 95% CI: 4,322–6,451) and whites (5,187 pg/mL; 95% CI: 3,938–6,832). Adjusted geometric mean leptin was nonstatistically significantly higher ( $P = 0.15$ ) in African Americans (5,954 pg/mL; 95% CI: 4,725–7,502) than in whites (4,133 pg/mL; 95% CI: 2,890–5,910). Conclusion: We observed a nonsignificantly higher adjusted cord blood leptin concentration in African-American male babies than in white male babies, although unadjusted levels were similar.

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## **Racial variation in umbilical cord blood leptin concentration in male babies**

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## ABSTRACT

**Background:** We hypothesize that racial differences *in utero* contribute to the racial disparity in prostate cancer risk. Leptin is a candidate for evaluating this hypothesis because it influences fetal development and newborn growth. **Methods:** We measured leptin concentration by ELISA in venous cord blood collected from 70 African-American and 37 white male full-term births. We measured sex steroid hormones and insulin-like growth factor (IGF) axis concentrations previously. Separately by race, we calculated the geometric mean leptin concentration and estimated the geometric mean adjusted for birth and placental weights, mother's age and parity, time of day and season of birth, and sex steroid hormone and IGF-axis concentrations using linear regression. **Results:** Leptin was positively correlated with birth ( $r=0.34$ ) and placental ( $r=0.25$ ) weights, IGF-1 ( $r=0.21$ ), and IGF binding protein-3 ( $r=0.29$ ) adjusting for race. Unadjusted geometric mean leptin did not differ ( $p=0.92$ ) between African Americans (5,280 pg/mL; 95% CI: 4,322-6,451) and whites (5,187 pg/mL; 95% CI: 3,938-6,832). Adjusted geometric mean leptin was nonstatistically significantly higher ( $p=0.15$ ) in African Americans (5,954 pg/mL; 95% CI: 4,725-7,502) than whites (4,133 pg/mL; 95% CI: 2,890-5,910). **Conclusion:** We observed a non-significantly higher adjusted cord blood leptin concentration in African-American compared with white male babies, although unadjusted levels were similar. **Impact:** These findings do not support the hypothesis that leptin level *in utero* contributes to the racial disparity in prostate cancer risk in adulthood.

## INTRODUCTION

In the US, African-American men have 1.6-times the incidence of and 2.4-times the mortality from prostate cancer compared with white men (1). Reasons for this disparity are unclear, but may include racial variation in dietary and lifestyle factors, health-seeking and treatment behaviors, and genetic susceptibility (2). This disparity remains after taking into account racial differences in the prevalence of exposures in middle age (3). That racial differences in exposures experienced in middle age do not appear to fully explain the disparity in prostate cancer rates supports investigating whether racial differences in exposures earlier in life may be explanatory.

Evidence is emerging that risk of chronic diseases (4), including cancer (5, 6), in adulthood may be influenced by the *in utero* environment. For example, in some studies higher birth weight, a marker for *in utero* development, has been reported to be associated with an increased risk of prostate cancer especially advanced stage disease (7-11). This observation suggests that growth-related factors *in utero* contribute to prostate carcinogenesis and may also influence the progression of the disease to a worse phenotype. Based on these findings, we hypothesize that racial differences in *in utero* factors, especially those that influence fetal development and newborn growth, may contribute to the observed racial disparity in prostate cancer.

Given our prior findings that African-American male babies had a higher molar ratio of testosterone to sex hormone binding globulin (SHBG) but lower concentrations of IGF-1 and IGF-2 in umbilical cord blood than white male babies (12), the hormone leptin was next of interest to us because of its role in fetal development and newborn growth (13). In adults, leptin, which is produced by adipose tissue, regulates energy

intake and expenditure (14). Relevant to racial disparities, circulating leptin levels were higher in African-American than white men taking into account differences in adiposity in a US nationally representative study (15). Although laboratory-based studies have shown that leptin promotes prostate cancer cell proliferation and angiogenesis (16), adult leptin levels have not been consistently associated with prostate cancer risk (17-21).

Relevant to the *in utero* environment, both fetal adipose tissue and the placenta produce leptin, and some fetal tissues and the placenta express the leptin receptor, suggesting an important role for leptin in the maintenance of pregnancy and fetal development (13, 22). In addition, *in utero* leptin levels may influence newborn growth via effects on the hypothalamus, which in turn may influence appetite regulation after birth and energy balance in adult life (23). Children who experience catch-up growth have been reported later in life to have a higher risk of obesity and the metabolic syndrome (24-26), both of which are risk factors for more aggressive prostate cancer in some studies (27).

Whether racial differences in leptin levels *in utero* exist and could, in part, explain the racial disparity in prostate cancer has not been addressed. Among the few studies that have evaluated differences in cord blood leptin concentrations between racial or ethnic groups (28, 29), none that we are aware of has compared cord blood leptin levels in African American and whites. African-American babies have a lower mean birth weight and a higher proportion of low and very low birth weight compared with white babies (30). Yet, African Americans have been reported to grow faster in childhood and early adolescence (31). While birth weight itself may not directly explain the higher risk

of prostate cancer in African-American men, *in utero* leptin levels could indirectly influence the risk of prostate cancer later in life through newborn or childhood catch-up growth. To begin to address this hypothesis, we evaluated whether venous umbilical cord blood leptin concentration differs between African-American and white male babies.

## **METHODS**

We used data and samples from the Hormones in Umbilical Cord Blood (HUB) Study; we reported details previously (12). The HUB Study was approved by the Institutional Review Boards (IRB) of the Prince George's Hospital Center and the Johns Hopkins Bloomberg School of Public Health. Evaluation of the leptin hypothesis using the HUB samples was approved by the Johns Hopkins Bloomberg School of Public Health IRB.

We collected venous umbilical cord blood samples from births that met inclusion criteria at two hospitals, Prince George's Hospital Center in Cheverly, MD (Hospital 1) and the Johns Hopkins Hospital in Baltimore, MD (Hospital 2), between February 2004 and June 2005. Delivery room nurses collected the cord blood samples and demographic data. Inclusion criteria for the babies were full-term birth (38<sup>th</sup>-42<sup>nd</sup> gestational week), normal birth weight (2,500-4,000 g), no major birth defects, and singleton birth. Inclusion criteria for the mothers were no pregnancy complications (e.g., gestational or pre-gestational diabetes mellitus, gestational or chronic hypertension, or thyroid diseases); no use of hormonal medications during pregnancy; and no known growth hormone deficiency. Also, the baby's mother and father were required to be of the same race.

For each eligible birth, the delivery room nurses used a standardized form to collect the following maternal and birth-related data: month and time (quadrant) of day of the birth, birth and placental weights, mother/child's race, and mother's age, parity (number of live births), and gravidity (number of pregnancies). The identities of the mothers and their babies were not recorded and no other information was collected. Fifteen milliliters of blood in total were collected into two tubes containing sodium EDTA from the umbilical cord vein. The samples were temporarily stored in a refrigerator and were usually processed within 12 hours. After centrifugation for 15 min at 2,400 rpm at room temperature, plasma, buffy coat, and red cells were aliquotted into cryovials and stored at -70°C.

The samples were randomly ordered for shipment and testing. Blinded quality control replicates of cord blood samples (n=6) were included to assess assay reliability. The plasma samples were shipped on dry ice by overnight courier to the laboratory of Dr. Nader Rifai at Children's Hospital Boston, MA. One hundred thirteen eligible male specimens were collected, 75 African Americans and 38 whites. After excluding 6 specimens missing on covariate data, the final analytic sample was 70 African Americans and 37 whites.

Leptin concentration was measured using an ultra-sensitive, enzymatically amplified, two-step sandwich-type immunoassay (R&D Systems, Minneapolis, MN). Laboratory technicians were blinded to race and hospital information. The lowest detection limit of the assay was 7.8 pg/mL. The coefficient of variation for the quality control specimens was 7.9%. Testosterone, estradiol, and SHBG were measured previously in the laboratory of Dr. Nader Rifai, Children's Hospital Boston, and IGF-1,

IGF-2, and IGFBP-3 were measured previously in the laboratory of Dr. Michael Pollak, Jewish General Hospital and McGill University (12).

Because leptin concentration was not normally distributed, we calculated the unadjusted geometric mean concentration and tested for a difference in concentration between the two racial groups using the t-test. To reduce possible confounding by the maternal and birth characteristics and the previously measured analytes, we evaluated whether the geometric means differed by race after adjusting for birth (continuous) and placental (continuous) weights, mother's age (continuous) and parity (indicator variables), time of day (indicator variables), season of birth (indicator variables), testosterone, estradiol, and SHBG (all indicator variables), and IGF-1, IGF-2, and IGF binding protein (BP)-3 (all indicator variables) using linear regression models. We tested for the difference in the prevalence of high leptin concentration ( $>10,000$  pg/mL) between the racial groups using the Cochran-Mantel-Haenszel test. All analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC).

## **RESULTS**

Characteristics of the mothers and their male babies are shown in Table 1. Compared with white mothers, African-American mothers were, on average, four years younger and were less likely to be nulliparous. Mean birth and placental weights were lower for African-American compared with white babies. Comparing African-American births between the two hospitals, mothers at Hospital 2 were more likely to be nulliparous and the distribution of the season, and time of day of birth differed.



Cord blood leptin concentration ranged from 354 to 75,333 pg/mL. Comparing cord blood leptin concentrations >10,000 pg/mL (the approximate 80<sup>th</sup> percentile) to at or below, the mothers were slightly older and were more likely to be multiparous and the birth and placental weights were slightly higher (data not shown). Leptin concentration was statistically significantly positively correlated with birth and placental weights, and concentrations of IGF-1, and IGFBP-3 adjusting for race (*Table 2*). In white babies, leptin concentration was positively correlated with birth weight and SHBG. In African-American babies, leptin was positively correlated with birth weight, placental weight, IGF-1, and IGFBP-3.

Median (inter-quartile range) cord blood leptin concentrations were 5,249 (3,443-9,579) and 4,999 (3,297-7,058) pg/mL in African-American and white male babies, respectively. Geometric mean cord blood leptin concentration ( $p=0.92$ ) did not differ between African-American (5,280 pg/mL; 95% CI: 4,322-6,451) and white (5,187 pg/mL; 95% CI: 3,938-6,832) male babies (*Table 3*). The prevalence of a high leptin concentration (>10,000 pg/mL) did not differ between African-American (22.9%) and white (18.9%) babies ( $p=0.64$ ). When we adjusted for maternal and birth characteristics, sex steroid hormones, and IGF-axis components simultaneously, cord blood leptin concentration was higher ( $p=0.15$ ) in African Americans (5,954 pg/mL; 95% CI: 4,725-7,502) compared with whites (4,133 pg/mL; 95% CI: 2,890-5,910). After multivariable adjustment, the prevalence of high leptin concentration differed between African-American and white babies ( $p<0.01$ ). Adjustment for birth weight and IGFBP-3 appeared to explain most of the difference between unadjusted and adjusted results when entering each maternal factor, birth factor, or other cord blood analytes into the

model one at a time. The results (data not shown) were similar to overall when restricting the analysis to the births at Hospital 2 only, and when restricting to mothers 20+ years old (the distribution of young maternal age differed by race).

## **DISCUSSION**

The purpose of this study was to evaluate whether umbilical cord blood leptin concentration differs by race, and if so, whether the direction of the difference could explain, in part, the observed racial disparity in prostate cancer incidence and mortality rates. Cord blood leptin concentration in male babies did not differ by race, although after adjustment for maternal and birth characteristics and concentrations of sex steroid hormones and IGF-axis components, leptin concentration appeared to be higher in African-Americans than whites. If our hypothesis were correct, we would have expected differences in cord blood leptin levels between African-American and white male babies in the unadjusted analysis as well.

Prior studies have evaluated racial differences in leptin levels in adulthood and childhood. Leptin concentration was similar in African-American and white men in three studies (32-34), but in two large studies, African-American men had higher leptin levels than white men when taking into account racial differences in body size (15, 35). When taking into account body size, leptin concentration was reported to be similar in pre-pubertal African-American and white children (36, 37) and in infants (38), or lower in African-American compared with white children and adolescents (39). Given the heterogeneity of the findings on racial variation, it is unclear whether our results for cord blood leptin are consistent or inconsistent with prior findings for adults and children.

In our study, African American babies had comparable unadjusted leptin levels despite their lower birth weight. Because leptin is hypothesized to influence growth after birth (23), it is possible that the higher leptin levels for a given birth weight may suggest a greater likelihood of catch-up growth among African-American babies compared with white babies. Babies who experience catch-up growth have a higher rate of fat gain than lean tissue gain (25) and are at an increased risk of diseases such as obesity and metabolic syndrome in later life (25, 26). However, whether the phenomenon of catch-up growth influences prostate cancer risk or influences the racial disparity in risk has yet to be evaluated, and no studies have reported low birth weight to be associated with an increased risk of prostate cancer (40).

We considered other possible alternative hypotheses that could account for not observing racial differences in cord blood leptin level in the unadjusted analysis. First, leptin exposure *in utero* may not play a role in prostate carcinogenesis and/or it does play a role but that it does not influence the racial disparity. Second, measurement of leptin in cord blood may not capture the etiologically relevant exposure *in utero* or the timing of when racial differences in leptin levels *in utero* may exist. Finally, we cannot rule out chance as an explanation for the lack of a racial difference in leptin level in the unadjusted analysis and/or the non-statistically significantly higher leptin level in African-Americans in the adjusted analysis.

To our knowledge, this is the first study to evaluate differences of cord blood leptin concentration between African-American and white males. We presented both unadjusted and adjusted results because they may lead to differing inferences. Unadjusted results reflect the levels experienced by the two racial groups, and if

different (barring lack of internal and external validity) could account for the racial disparity in prostate cancer risk in the population. In contrast, the adjusted results reflect whether there may be racial variation in leptin levels beyond known factors that influence leptin levels and that differ by race, including inherent racial differences. We were able to adjust for maternal and birth characteristics, sex steroid hormones, and components of the IGF-axis, analytes that we previously found to differ by race in the cord blood of males (12). However, we did not collect information on the mothers' diet and lifestyle or assess maternal leptin levels during pregnancy. Our study was powered to detect moderate or large differences by race in cord blood biomarker concentrations (12). Because the sample size for African-American males was larger for white males, correlations of similar magnitude were statistically significant in African-Americans, but not in whites.

Because we conducted the study at only two hospitals, imposed inclusion criteria and do not know the proportion of all eligible male births that were included in the study, it is unclear whether our cord blood leptin results are generalizable to other births at the two hospitals or to US African-American and white male babies. Nevertheless, cord blood leptin concentration was in the range previously reported for US babies whose birth weight was appropriate for gestational age (41, 42), including in a study of full-term African-American babies unselected for birth weight (43). Further, the applicability of our results from this contemporary birth cohort to the birth cohorts that are now in the age range to be at risk for prostate cancer and that are now experiencing the racial disparity is unknown.

In conclusion, we observed no difference in cord blood leptin concentration between African-American and white male babies, although after taking into account maternal and birth characteristics, sex steroid hormones, and IGF axis components, the level was non-statistically significantly higher in African Americans. That African-American male babies had similar leptin concentration to whites in the unadjusted analysis does not support the hypothesis that leptin level *in utero* contributes to the racial disparity in prostate cancer risk in adulthood.

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Table 1. Maternal and birth characteristics by race and hospital, males, HUB Study 2004-2005

	African-American			White	<i>p</i> -value		
	Hospital 1	Hospital 2	Hospital 1 & 2	Hospital 2	African-American, Hospital 1 vs 2	African-American vs white, Hospital 2	African-American vs white
N	33	37	70	37			
Mother's age (years; mean, sd)	24.4 (5.0)	24.0 (7.1)	24.2 (6.2)	28.7 (6.3)	0.77 <sup>a</sup>	0.004 <sup>a</sup>	<0.001 <sup>a</sup>
Baby's birth weight (g; mean, sd)	3286 (316)	3193 (362)	3237 (342)	3477 (395)	0.26 <sup>a</sup>	0.002 <sup>a</sup>	0.001 <sup>a</sup>
Placental weight (g; mean, sd)	673 (152)	641 (118)	656 (135)	698 (153)	0.33 <sup>a</sup>	0.08 <sup>a</sup>	0.15 <sup>a</sup>
Parity (%)							
0	15.2	40.5	28.6	62.2	0.10 <sup>b</sup>	0.21 <sup>b</sup>	0.009 <sup>b</sup>
1	45.5	27	35.7	21.6			
2	21.2	13.5	17.1	10.8			
≥3	18.2	18.9	18.6	5.4			
Season of birth (%)							
Winter	36.4	24.3	30	10.8	<0.001 <sup>b</sup>	0.05 <sup>b</sup>	0.04 <sup>b</sup>
Spring	27.3	73	51.4	67.6			
Summer	6.1	0	2.9	10.8			
Fall	30.3	2.7	15.7	10.8			
Time of day of birth (%)							
Midnight, <6 am	3	27	15.7	32.4	<0.001 <sup>b</sup>	0.20 <sup>b</sup>	0.001 <sup>b</sup>
6 am, <noon	42.4	27	34.3	8.1			
Noon, <6 pm	51.5	21.6	35.7	24.3			
6pm, <midnight	3	24.3	14.3	35.1			

<sup>a</sup> T-test<sup>b</sup> Fisher's exact test

Table 2. Correlations<sup>a</sup> between umbilical cord blood leptin concentration and maternal and birth characteristics, sex steroid hormones, and growth factors, overall and by race, males, HUB Study 2004-2005

	All (n=107) <sup>b</sup>		White (n=37)		African-American (n=70)	
	Leptin	<i>p</i> -value	Leptin	<i>p</i> -value	Leptin	<i>p</i> -value
Mother's age	0	0.98	0.06	0.73	-0.02	0.87
Parity	0.04	0.65	0.19	0.27	-0.04	0.76
Birth weight	0.34	<b>0.0003</b>	0.49	<b>0.0022</b>	0.28	<b>0.02</b>
Placental weight	0.25	<b>0.01</b>	0.23	0.16	0.25	<b>0.04</b>
IGF-1	0.21	<b>0.02</b>	0.1	0.54	0.28	<b>0.02</b>
IGF-2	0.11	0.25	0.19	0.25	0.12	0.32
IGFBP-3	0.29	<b>0.0025</b>	0.22	0.2	0.36	<b>0.0026</b>
Testosterone	0.11	0.25	-0.02	0.89	0.16	0.18
Estradiol	-0.07	0.49	0.08	0.65	-0.14	0.24
SHBG	0.03	0.73	0.4	<b>0.01</b>	-0.14	0.25

<sup>a</sup> Spearman correlation coefficients

<sup>b</sup> Adjusted for race

Table 3. Geometric mean umbilical cord blood leptin concentration (pg/mL) by race, males, HUB Study 2004-2005

	White		African-American		<i>p</i> -value
	Geometric mean	95% CI	Geometric mean	95% CI	
Unadjusted	5,187	3,938-6,832	5,280	4,322-6,451	0.92
Adjusted for					
Birth and placental weights, mother's age and parity, season and time of day of birth	4,434	3,209-6,126	5,737	4,621-7,122	0.11
Testosterone, estradiol, SHBG	4,726	3,514-6,357	5,546	4,496-6,842	0.41
IGF-1, IGF-2, IGFBP-3	4,691	3,555-6,189	5,568	4,576-6,776	0.34
Birth and placental weights, mother's age and parity, season and time of day of birth, testosterone, estradiol, SHBG	4,046	2,858-5,727	6,021	4,795-7,562	0.1
Birth and placental weights, mother's age and parity, season and time of day of birth, IGF-1, IGF-2, IGFBP-3	4,302	3,081-6,006	5,829	4,684-7,254	0.19
Birth and placental weights, mother's age and parity, season and time of day of birth, testosterone, estradiol, SHBG, IGF-1, IGF-2, IGFBP-3	4,133	2,890-5,910	5,954	4,725-7,502	0.15